

CLAIMS

1. A method for micronizing a hydrophobic agent, comprising:
dissolving a hydrophobic agent in an effective amount of a first solvent, wherein the
5 first solvent is free of polymer, wherein the hydrophobic agent and the solvent form a mixture
having a continuous phase,
introducing a second solvent into the mixture, and
introducing an aqueous solution into the mixture wherein the aqueous solution causes
precipitation of the hydrophobic agent to produce a composition of micronized hydrophobic
10 agent having an average particle size of 1 micron or less.
2. The method of claim 1, further comprising preparing microparticles by spray
drying the micronized hydrophobic agent.
- 15 3. The method of claim 1, further comprising preparing microparticles of the
micronized hydrophobic agent by a method selected from the group consisting of: spray
drying, interfacial polymerization, hot melt encapsulation, phase separation encapsulation,
spontaneous emulsion, solvent evaporation microencapsulation, solvent removal
microencapsulation, coacervation, and low temperature microsphere formation.
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4. The method of claim 1, further comprising preparing microparticles by
performing phase inversion nanoencapsulation (PIN) on the micronized hydrophobic agent.
- 25 5. The method of claim 1, wherein the second solvent is an alcohol, and wherein
the alcohol is selected from the group consisting of: methanol (methyl alcohol), ethanol,
(ethyl alcohol), 1-propanol (n-propyl alcohol), 2-propanol (isopropyl alcohol), 1-butanol (n-
butyl alcohol), 2-butanol (sec-butyl alcohol), 2-methyl-1-propanol (isobutyl alcohol), 2-
methyl-2-propanol (t-butyl alcohol), 1-pentanol (n-pentyl alcohol), 3-methyl-1-butanol
(isopentyl alcohol), 2,2-dimethyl-1-propanol (neopentyl alcohol), cyclopentanol (cyclopentyl
30 alcohol), 1-hexanol (n-hexanol), cyclohexanol (cyclohexyl alcohol), 1-heptanol (n-heptyl
alcohol), 1-octanol (n-octyl alcohol), 1-nonanol (n-nonyl alcohol), 1-decanol (n-decyl
alcohol), 2-propen-1-ol (allyl alcohol), phenylmethanol (benzyl alcohol), diphenylmethanol
(diphenylcarbinol), triphenylmethanol (triphenylcarbinol), glycerin, phenol, 2-

methoxyethanol, 2-ethoxyethanol, 3-ethoxy-1,2-propanediol, di(ethylene glycol) methyl ether, 1,2-propanediol, 1,3-propanediol, 1,3-butanediol, 2,3-butanediol, 1,4-butanediol, 1,2-pentanediol, 1,3-pentanediol, 1,4-pentanediol, 1,5-pentanediol, 2,3-pentanediol, 2,4-pentanediol, 2,5-pentanediol, 3,4-pentanediol, and 3,5-pentanediol.

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6. The method of claim 5, wherein the alcohol is isopropanol.

7. The method of claim 1, wherein the second solvent is a mixture of alcohols.

10 8. The method of claim 7, wherein the mixture of alcohols comprises:
two or more of the alcohols selected from the group consisting of: methanol (methyl
alcohol), ethanol, (ethyl alcohol), 1-propanol (n-propyl alcohol), 2-propanol (isopropyl
alcohol), 1-butanol (n-butyl alcohol), 2-butanol (sec-butyl alcohol), 2-methyl-1-propanol
(isobutyl alcohol), 2-methyl-2-propanol (t-butyl alcohol), 1-pentanol (n-pentyl alcohol), 3-
15 methyl-1-butanol (isopentyl alcohol), 2,2-dimethyl-1-propanol (neopentyl alcohol),
cyclopentanol (cyclopentyl alcohol), 1-hexanol (n-hexanol), cyclohexanol (cyclohexyl
alcohol), 1-heptanol (n-heptyl alcohol), 1-octanol (n-octyl alcohol), 1-nonanol (n-nonyl
alcohol), 1-decanol (n-decyl alcohol), 2-propen-1-ol (allyl alcohol), phenylmethanol (benzyl
alcohol), diphenylmethanol (diphenylcarbinol), triphenylmethanol (triphenylcarbinol),
20 glycerin, phenol, 2-methoxyethanol, 2-ethoxyethanol, 3-ethoxy-1,2-propanediol, di(ethylene
glycol) methyl ether, 1,2-propanediol, 1,3-propanediol, 1,3-butanediol, 2,3-butanediol, 1,4-
butanediol, 1,2-pentanediol, 1,3-pentanediol, 1,4-pentanediol, 1,5-pentanediol, 2,3-
pentanediol, 2,4-pentanediol, 2,5-pentanediol, 3,4-pentanediol, and 3,5-pentanediol.

25 9. The method of claim 1, wherein greater than 90% of the micronized
hydrophobic agent have a particle size less than 1 micron.

10. The method of claim 1, wherein the hydrophobic agent is dissolved by heating
the hydrophobic agent in the first solvent.

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11. The method of claim 1, wherein the hydrophobic agent is dissolved by
sonicating the hydrophobic agent in the first solvent.

12. The method of claim 1, wherein the hydrophobic agent is dissolved by high shearing the hydrophobic agent in the first solvent.

13. The method of claim 1, wherein the hydrophobic agent is dissolved by high stirring the hydrophobic agent in the first solvent.

14. A method for micronizing a hydrophobic agent, comprising:
dissolving a hydrophobic agent in an effective amount of a first solvent, with a polymer, wherein the hydrophobic agent and the first solvent form a mixture having a continuous phase, introducing a second solvent into the mixture, and introducing an aqueous solution into the mixture wherein the aqueous solution causes precipitation of the hydrophobic agent to produce a composition of micronized hydrophobic agent having an average particle size of 1 micron or less.

15. The method of claim 14, wherein the preparation contains less than 5% polymer.

16. The method of claim 14, wherein the polymer is removed by the aqueous solution.

17. The method of claim 14, further comprising preparing microparticles by spray drying the micronized hydrophobic agent.

18. The method of claim 14, further comprising preparing microparticles of the micronized hydrophobic agent by a method selected from the group consisting of: interfacial condensation, hot melt encapsulation, and phase separation encapsulation.

19. The method of claim 14, further comprising preparing microparticles by performing phase inversion nanoencapsulation on the micronized hydrophobic agent.

20. The method of claim 14, wherein the second solvent is an alcohol.

21. The method of claim 20, wherein the alcohol is selected from the group consisting of: methanol (methyl alcohol), ethanol, (ethyl alcohol), 1-propanol (n-propyl alcohol), 2-propanol (isopropyl alcohol), 1-butanol (n-butyl alcohol), 2-butanol (sec-butyl alcohol), 2-methyl-1-propanol (isobutyl alcohol), 2-methyl-2-propanol (t-butyl alcohol), 1-pentanol (n-pentyl alcohol), 3-methyl-1-butanol (isopentyl alcohol), 2,2-dimethyl-1-propanol (neopentyl alcohol), cyclopentanol (cyclopentyl alcohol), 1-hexanol (n-hexanol), cyclohexanol (cyclohexyl alcohol), 1-heptanol (n-heptyl alcohol), 1-octanol (n-octyl alcohol), 1-nonanol (n-nonyl alcohol), 1-decanol (n-decyl alcohol), 2-propen-1-ol (allyl alcohol), phenylmethanol (benzyl alcohol), diphenylmethanol (diphenylcarbinol), triphenylmethanol (triphenylcarbinol), glycerin, phenol, 2-methoxyethanol, 2-ethoxyethanol, 3-ethoxy-1,2-propanediol, di(ethylene glycol) methyl ether, 1,2-propanediol, 1,3-propanediol, 1,3-butanediol, 2,3-butanediol, 1,4-butanediol, 1,2-pentanediol, 1,3-pentanediol, 1,4-pentanediol, 1,5-pentanediol, 2,3-pentanediol, 2,4-pentanediol, 2,5-pentanediol, 3,4-pentanediol, and 3,5-pentanediol.

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22. The method of claim 20, wherein the alcohol is isopropanol.

23. The method of claim 14, wherein the second solvent is a mixture of alcohols.

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24. The method of claim 23, wherein the mixture of alcohols comprises:

two or more of the alcohols selected from the group consisting of: methanol (methyl alcohol), ethanol, (ethyl alcohol), 1-propanol (n-propyl alcohol), 2-propanol (isopropyl alcohol), 1-butanol (n-butyl alcohol), 2-butanol (sec-butyl alcohol), 2-methyl-1-propanol (isobutyl alcohol), 2-methyl-2-propanol (t-butyl alcohol), 1-pentanol (n-pentyl alcohol), 3-methyl-1-butanol (isopentyl alcohol), 2,2-dimethyl-1-propanol (neopentyl alcohol), cyclopentanol (cyclopentyl alcohol), 1-hexanol (n-hexanol), cyclohexanol (cyclohexyl alcohol), 1-heptanol (n-heptyl alcohol), 1-octanol (n-octyl alcohol), 1-nonanol (n-nonyl alcohol), 1-decanol (n-decyl alcohol), 2-propen-1-ol (allyl alcohol), phenylmethanol (benzyl alcohol), diphenylmethanol (diphenylcarbinol), triphenylmethanol (triphenylcarbinol), glycerin, phenol, 2-methoxyethanol, 2-ethoxyethanol, 3-ethoxy-1,2-propanediol, di(ethylene glycol) methyl ether, 1,2-propanediol, 1,3-propanediol, 1,3-butanediol, 2,3-butanediol, 1,4-butanediol, 1,2-pentanediol, 1,3-pentanediol, 1,4-pentanediol, 1,5-pentanediol, 2,3-pentanediol, 2,4-pentanediol, 2,5-pentanediol, 3,4-pentanediol, and 3,5-pentanediol.

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25. The method of claim 14, wherein greater than 90% of the micronized hydrophobic agent have a particle size less than 1 micron.

5 26. The method of claim 14, wherein the hydrophobic agent is dissolved by heating the hydrophobic agent in the first solvent.

27. The method of claim 14, wherein the hydrophobic agent is dissolved by sonicating the hydrophobic agent in the first solvent.

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28. The method of claim 14, wherein the hydrophobic agent is dissolved by high shearing the hydrophobic agent in the first solvent.

29. The method of claim 14, wherein the hydrophobic agent is dissolved by high stirring the hydrophobic agent in the first solvent.

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30. A preparation of micronized hydrophobic agent prepared according to the method of any one of claims 1-13.

20 31. A preparation of micronized hydrophobic agent prepared according to the method of any one of claims 14-29.

32. A composition, comprising a preparation of micronized hydrophobic agent having an average particle size of less than 1 micron, wherein the preparation is composed of less than 5% polymer carrier and is free of surfactant.

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33. The composition of claim 32, wherein the preparation is free of polymer carrier.

30 34. A composition, comprising a preparation of micronized hydrophobic agent having an average particle size of less than 1 micron, wherein the preparation is free of polymer carrier and wherein the crystallinity of the micronized hydrophobic agent is at least 50% of the crystallinity of the non-micronized hydrophobic agent.

35. The composition of claim 34, wherein the crystallinity is at least 75%.
36. The composition of claim 34, wherein the crystallinity is greater than 90%.
- 5 37. A method for delivering an agent to a subject, comprising:
orally administering a solid preparation of micronized hydrophobic agent having an
average particle size of less than 1 micron, wherein the preparation is composed of less than
5% polymer and is free of surfactant.
- 10 38. The method of claim 37, wherein the bioactivity of the hydrophobic agent is
retained.
39. The method of claim 37, wherein there is at least a 5% increase in the relative
15 bioavailability of the micronized hydrophobic agent as compared to the non-micronized
hydrophobic agent.
40. The method of claim 37, wherein the preparation is free of polymer.
- 20 41. The method of claim 37, wherein the micronized hydrophobic agent is
microencapsulated by phase inversion nanoencapsulation.
42. A method for delivering an agent to a subject, comprising:
administering microparticles of a micronized hydrophobic agent encapsulated by
25 phase inversion nanoencapsulation having an average particle size of less than 1 micron,
wherein the preparation is composed of less than 5% polymer and is free of surfactant.
43. The method of claim 42, wherein the microparticles are administered orally.
- 30 44. The method of claim 42, wherein the bioactivity of the hydrophobic agent is
retained.

45. The method of claim 42, wherein there is at least a 5% increase in the relative bioavailability of the micronized hydrophobic agent as compared to the non-encapsulated micronized hydrophobic agent.

5 46. The method of claim 42, wherein the preparation is free of polymer.

47. A method for achieving 100% bioactivity comprising:
orally administering to the subject a solid preparation of micronized hydrophobic agent having an average particle size of less than 1 micron and wherein 100% of the orally
10 administered agent is bioactive.

48. The method of claim 47, wherein the preparation is composed of less than 5% polymer and is free of surfactant.

15 49. The method of claim 47, wherein the preparation is free of polymer.